Serial Measurements of Structural Connectivity and Diffusion-Tensor Metrics in Parkinson's Disease

Andre Ticlo[1], Sofia Reimão[2], Hugo Alexandre Ferreira[1], João Marcos Sousa[1], Daisy Abreu[3], Joaquim Ferreira[3], Jorge Campos[2], and Rita Gouveia Nunes[1]
[1]Instituto de Biofisica e Engenharia Biomedica, Faculdade de Ciencias, Universidade de Lisboa, Lisbon, Portugal, [2]Neurological Imaging Department of Hospital Santa Maria, Centro Hospitalar Lisboa Norte, Lisbon, Portugal, [3]Clinical Pharmacology Unit, Instituto de Medicina Molecular, Lisbon, Portugal

TARGET AUDIENCE: Neuroimaging, neuroscience researchers and clinicians interested in Parkinson's disease, diffusion imaging and brain connectivity.

PURPOSE: Many studies focusing on Parkinson's disease (PD) have compared diffusion metrics, such as Fractional Anisotropy (FA) and Mean Diffusivity (MD) in healthy subjects versus PD patients[1] but, as far as we are aware, no previous studies looked into how these metrics evolve with disease duration. Recently, there has been a lot of interest in applying graph theory to characterize brain connectivity[2,3] including in PD[4]. We imaged a group of PD patients and a control group over a period of 1 year. Changes in diffusion values (FA and MD) and connectivity metrics were investigated after evaluating the reproducibility of the methodology.

ROI	Group	Scan	FA		*p*-value	MD × 10^{-3} mm/s^2		*p*-value
			Median	Range		Median	Range	
Left caudal middle frontal cortex	PD	MR_{first}	0.22	0.14	**0.04**	1.14	0.433	0.25
		MR_{1year}	0.20	0.09		1.01	0.391	
	Control	MR_{first}	0.17	0.08	0.75	1.10	0.416	0.12
		MR_{1year}	0.18	0.04		0.97	0.202	
Left amygdala	PD	MR_{first}	0.27	0.05	**0.04**	1.12	1.48	0.46
		MR_{1year}	0.26	0.09		0.96	0.58	
	Control	MR_{first}	0.27	0.08	0.12	0.87	0.27	0.46
		MR_{1year}	0.27	0.05		0.82	0.11	
Left putamen	PD	MR_{first}	0.27	0.07	**0.04**	0.81	0.35	0.51
		MR_{1year}	0.29	0.05		0.79	0.12	
	Control	MR_{first}	0.30	0.09	0.75	0.75	0.09	0.17
		MR_{1year}	0.29	0.06		0.74	0.03	
Left accumbens	PD	MR_{first}	0.27	0.05	0.50	1.22	1.24	**0.046**
		MR_{1year}	0.28	0.11		0.93	0.33	
	Control	MR_{first}	0.25	0.15	0.46	1.07	0.90	0.35
		MR_{1year}	0.27	0.09		0.92	0.40	
Left thalamus	PD	MR_{first}	0.35	0.10	0.23	0.97	0.53	0.05
		MR_{1year}	0.37	0.09		0.81	0.16	
	Control	MR_{first}	0.35	0.16	0.46	0.85	0.60	0.46
		MR_{1year}	0.38	0.06		0.78	0.06	
Left hippocampus	PD	MR_{first}	0.23	0.08	0.14	1.34	0.81	**0.046**
		MR_{1year}	0.21	0.15		1.12	0.23	
	Control	MR_{first}	0.23	0.09	0.17	1.11	0.53	0.75
		MR_{1year}	0.21	0.03		1.12	0.13	
Right medial orbito-frontal cortex	PD	MR_{first}	0.24	0.05	0.50	1.14	0.54	**0.047**
		MR_{1year}	0.27	0.09		1.01	0.19	
	Control	MR_{first}	0.23	0.07	0.60	1.05	0.20	0.60
		MR_{1year}	0.23	0.03		1.06	0.23	
Right amygdala	PD	MR_{first}	0.24	0.08	0.35	1.22	1.8	**0.03**
		MR_{1year}	0.26	0.09		0.87	0.18	
	Control	MR_{first}	0.26	0.06	0.75	0.83	0.18	0.92
		MR_{1year}	0.26	0.07		0.85	0.24	
Right pallidum	PD	MR_{first}	0.34	0.24	0.49	1.05	1.92	**0.03**
		MR_{1year}	0.37	0.11		0.72	0.13	
	Control	MR_{first}	0.36	0.14	0.34	0.76	0.44	0.25
		MR_{1year}	0.37	0.08		0.75	0.16	
Right cuneus	PD	MR_{first}	0.18	0.09	0.69	1.21	0.32	**0.03**
		MR_{1year}	0.17	0.07		1.05	0.17	
	Control	MR_{first}	0.15	0.04	0.35	1.08	0.22	0.17
		MR_{1year}	0.16	0.02		1.03	0.10	
Right precuneus	PD	MR_{first}	0.21	0.06	0.14	0.97	0.30	**0.03**
		MR_{1year}	0.21	0.18		0.89	0.18	
	Control	MR_{first}	0.18	0.05	0.35	0.94	0.12	**0.04**
		MR_{1year}	0.19	0.03		0.83	0.10	

Table 1: Fractional Anisotropy and Mean Diffusivity for PD patients and controls measured at two acquisition times; *p*-values obtained using the Mann-Whitney test (significant values in bold).

METHODS: Two groups were studied: PD (age 66.5±6.4, 8 males/4 females) diagnosed 2 to 5 years prior to the study and a Control group (age 62.1 ±6.7, 5 males/6 females). Each subject had diffusion-weighted (DW) MRI scans at 3 distinct times: MR_{first} and $MR_{inscanner}$ on the same day and MR_{1year} acquired 1 year later. Images were acquired on a Philips Achieva® 3.0 T including DW Single Shot Echo Planar Imaging with one non-DW image and 32 diffusion directions, b-value of 1000 s/mm^2, reconstruction matrix 256×256, slice thickness 1.5 mm, TE/TR 64/7703 ms, FOV 240×240 mm^2, 60 slices. A T1-weighted Spoiled Gradient Echo (SPG) image was also acquired: reconstruction matrix 512×512, slice thickness 1.5 mm, TE/TR 4.6/9.4 ms, FOV 240×240 mm^2, 60 slices. Regarding the DW images, the FSL[5] (www.fmrib.ox.ac.uk/fsl) tool *eddy* was used for eddy current distortion correction, and *dtifit*[6] for estimating the diffusion tensor, FA and MD. The brain extraction tool[5] was used to remove non-brain tissues. The DW images were registered to standard MNI space (1 mm^3 resolution) using the SPG image as an intermediate target with *Flirt* and *Fnirt*[5]. Segmentation of SPG images was performed with Freesurfer (http://surfer.nmr.mgh.harvard.edu/), the cortical and sub-cortical Regions of Interest (ROI) were transformed into DW-space and the mean and standard deviation of FA and MD measured within each ROI. White matter streamlines were estimated using DTK (Diffusion Toolkit)[7]. These were used as input to the MIBCA toolbox[8] to obtain the adjacency matrices, and the connectivity metrics calculated using the brain connectivity toolbox[3]. Local metrics included: node degree, clustering coefficient, local efficiency and betweenness centrality. As for tested global metrics, these were: global efficiency and transitivity. A reproducibility study was performed comparing FA, MD, local and global connectivity metrics between MR_{first} and $MR_{inscanner}$ (from both weighted and matrices binarized with varying threshold levels).

Group	Scan	G. Efficiency	
		Median	Range
PD	MR_{first}	0.20	0.11
	$MR_{inscanner}$	0.19	0.10
	MR_{1year}	0.19	0.23
Controls	MR_{first}	0.22	0.13
	$MR_{inscanner}$	0.24	0.10
	MR_{1year}	0.23	0.09
Acq./Group	**Test**	***p*-value**	
MR_{first}	PD vs Controls	0.37	
PD	MR_{first} vs MR_{1year}	0.46	
Controls	MR_{first} vs MR_{1year}	0.09	

Table 2: Global efficiency for PD patients and controls for the three scans; *p*-values for comparisons between groups or acquisitions (Wilcoxon signed rank test).

Statistical analysis was performed using the R Software (www.r-project.org). Reproducibility was evaluated computing the Intra-Class Correlation (ICC) with 0.7 set as the minimum acceptable. Wilcoxon signed rank tests (significance level of 0.05) were used to assess changes between MR_{first} and MR_{1year} for each subject group. The Mann-Whitney test (significance of 0.05) was used for comparisons between groups.

RESULTS: Diffusion metrics were reproducible between the two runs for all ROIs (min ICC of 0.71). Global efficiency was found to be reproducible between MR_{first} and $MR_{inscanner}$ only when using matrices binarized with a threshold of 150 streamlines connecting pairs of ROIs (min ICC of 0.75). Since transitivity (min ICC of 0.02) and the local metrics were not sufficiently reproducible (minimum difference between MR_{first} and $MR_{inscanner}$ of 70% of their mean), they were not calculated for MR_{1year}. Several differences were found over time for diffusion metrics (Table 1). For the PD group FA values were significantly changed after one year in the caudal middle frontal cortex, amygdala and putamen (left hemisphere) and decreased MD was measured in the medial orbito-frontal cortex (right hemisphere). Furthermore, decreased MD was found in the right pallidum and left accumbens and also in the left thalamus and hippocampus, right amygdala, cuneus and precuneus. Only one region (right precuneus) showed changes in the control group indicating that the changes observed in the PD group are probably disease related. The affected areas are consistent with previous PD studies[1] and the results compatible with a higher level of conscious planning required for PD patients to perform standard movements such as walking.

Regarding the structural connectivity metrics, although global efficiency did not vary significantly over time or between groups, the median global efficiency was consistently lower for PD patients (Table 2). This metric measures how efficiently information is transmitted between nodes, and so a decrease in global efficiency could reflect structural changes in these patients, compatible with their symptoms: for instance the loss of motor capabilities due to impaired connectivity.

CONCLUSIONS: Diffusion metrics can be used to evaluate structural changes in PD patients over time. FA and MD changes in frontal cortical regions indicate a compensation for the loss of connectivity within the normal motor pathways. As for brain connectivity metrics, although we did not find significant differences, results suggest that global efficiency is a promising biomarker for monitoring PD progression, although great care should be taken to ensure reproducibility of the measurements. The reproducibility of connectivity metrics should be evaluated for alternative tractography approaches. Further studies with more subjects and a longer disease duration should be performed to confirm our observations.

REFERENCES: **1**-Cochrane CJ, et al Neurology, 2013;80:857-64; **2-** Junning Li,Z et al: ISBI, 2006;964-9; **3**- Rubinov M and Sporns O, NeuroImage, 2010;52:1059–69, **4-** Sousa JM et al., ISMRM 2014;22:1921; **5-** Jenkinson M et al. NeuroImage, 2012;62:782–790; **6**-Behrens TEJ et al, MRM, 2003;50:1077–88; 7-Wang R and Benner T. ISMRM,2007;15:3720; **8-** Ribeiro A et al., MAGMA,2013;26:232.

ACKNOWLEDGMENTS: Fundação para a Ciência e Tecnologia FCT/MCE (PIDDAC) under grant PTDC/SAU-ENB/120718/2010.